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JEAN-LOUIS, SAMIRA JM	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/560,669
Filing Date: March 23, 2007
Appellant(s): COUTRE, STEVEN

George Dohmann
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 07/16/10 appealing from the Office action mailed on 12/17/09.

The appeal brief is filed in the new format under the revised BPAI final rule before the effective date of the BPAI final rule. The Office published the BPAI final rule to amend the rules governing practice before the BPAI in *ex parte* patent appeals. *See Rules of Practice Before the Board of Patent Appeals and Interferences in Ex Parte Appeals; Final Rule, 73 FR 32938 (June 10, 2008), 1332 Off. Gaz. Pat. Office 47 (July 1, 2008).* However, the effective date for the BPAI final rule has been delayed. *See Rules of Practice Before the Board of Patent Appeals and Interferences in Ex Parte Appeals; Delay of Effective and Applicability Dates, 73 FR 74972 (December 10, 2008).* In the notice published on November 20, 2008, the Office indicated that the Office will not hold an appeal brief as non-compliant solely for following the new format even though it is filed before the effective date. *See Clarification of the Effective Date Provision in the Final Rule for Ex parte Appeals, 73 FR 70282 (November20, 2008).* Since the appeal brief is otherwise acceptable, the Office has accepted the appeal brief filed by appellant.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 20-39 are currently pending and stand rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(8) Evidence Relied Upon

Longley et al. Hematology & Oncology Clinics of North America, Vol. 14, No. 3, pgs. 689-695.

Goekjian et al. Experts Opinions on Investigational Drugs, December 2001, Vol. 10, No. 12, pgs. 2117-2140.

Ma et al. Blood, 2002, Vol. 99, No. 5, pgs. 1741-1744.

5,093,330	Cavaratti	3-1992
20020061873	Matthews	5-2002

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 20 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Longley et al. (Hematology/Oncology Clinics of North America,, Vol. 14, No. 3, pgs. 689-695, previously cited) in view of Goekjian et al. (Experts Opinions on Investigational Drugs, December 2001, Vol. 10, No. 12, pgs. 2117-2140, previously submitted).

Longley et al. teach that the treatment of mastocytosis is designed to prevent or ameliorate the deleterious effects of mast cell mediators rather than to eliminate the mast cells which produce and release them (see pg. 689). Longley et al. further teach that current forms of therapy while they lead to a decrease of mast cell numbers also cause significant adverse side effects (see pg. 690, paragraph 2). However, recent studies have suggested that mutations affecting the protein coding region of the c-kit proto-oncogene may cause some forms of mastocytosis (see pg. 690, paragraph 3). Specifically, Longley teaches that one group consists of mutations in codon 816 of human c-kit or its equivalent positions in other species, resulting in single residue substitution for Asp816 in the activation loop of the receptor kinase domain (pg. 691). C-kit encodes a receptor tyrosine kinase whose cognate ligand is mast cell growth

factor. Activation of mast cell growth factor receptor or kit stimulates mast cell growth and prevents apoptosis. Furthermore, activating mutations have been found as somatic mutations in the neoplastic mast cells of patients with mastocytosis. Thus, the consistent finding of activating c-kit mutations in mast cell tumors, together with the ability of activated kit to stimulate mast cell proliferation and transformation, suggests that these mutations are necessary if not sufficient, for some forms of mastocytosis (see pg. 690, last paragraph). Moreover, Longley et al. teach that inhibiting activating kit with kit inhibitors might be therapeutically useful in mastocytosis, might provide symptoms relief, decrease mast cell load and might eventually provide a cure by completely eliminating the neoplastic mast cell clone (see pg. 690, last paragraph). Additionally, Longley et al. demonstrated that kit kinase inhibitors can effectively kill neoplastic mast cells which cause some forms of mastocytosis by using various kit inhibitors and demonstrating their various levels of inhibition in both wild type kit and p815 mutant cells (i.e. cells possessing mutation equivalent to D816V; see pg. 693, last paragraph and figs. 1-2).

Longley et al. do not specifically teach midostaurin or PKC412 as the kit kinase inhibitor effective in treating mastocytosis.

Goekjian et al. teach midostaurin or PKC-412 as an inhibitor of PKC that effectively inhibit signal transduction pathways (see pg. 2117, abstract). Goekjian et al. also teach that first generation staurosporine analogues CGP41251 or PKC-412 or

midostaurin achieves a greater level of kinase selectivity and potential therapeutic index as a PKC inhibitor and tends to be non-toxic in light of mixed kinase inhibition that it exhibits (see pg. 2123. right col., last paragraph). Importantly, Goekjian et al. teach that midostaurin is a broad range kinase inhibitor and has been found to inhibit the stem cell factor receptor c-kit at approximately micromolar concentration (i.e. midostaurin is a kit inhibitor; see pg. 2124, table 1 and Section 3.1).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the midostaurin of Goekjian et al. for the treatment of mastocytosis since Goekjian et al. teach midostaurin as a non-toxic kit inhibitor and Longley et al. teach that mastocytosis can be best treated with kit inhibitors. Thus, given the teachings of Longley and Goekjian, one of ordinary skill would have been motivated to try and motivated to utilize midostaurin in light of the disclosures of Goekjian and Longley with the reasonable expectation of providing a method effective in treating mastocytosis with a low toxicity staurosporine derivative.

Claims 30 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Longley et al. (Hematology/Oncology Clinics of North America,, Vol. 14, No. 3, pgs. 689-695, previously cited) in view of Goekjian et al. (Experts Opinions on Investigational Drugs, December 2001, Vol. 10, No. 12, pgs. 2117-2140, previously submitted) as applied to claim 20 above and in further view of Ma et al. (Blood, 2002, Vol. 99, No. 5, pgs. 1741-1744, previously cited).

The Goekjian and Longley references are as discussed above and incorporated by reference herein. However, Goekjian and Longley do not teach treatment of mastocytosis resistant to imatinib.

Ma et al., however, teach that adult-type or sporadic adult-type human mastocytosis (SAHM) is characterized by mutations in c-kit codon 816, which causes constitutive activation of the KIT kinase (i.e. D186v mutant kit or c-kit; see pg. 1741, left col. paragraph 1). Ma et al. also teach that mast cell lines and canine mast cell tumors also express activating c-kit mutations and small molecules that inhibit mutant activated KIT was able to effectively kill these cell lines (see pg. 1741, left col., paragraph 1). Ma et al. further teach that STI571 (i.e. imatinib) while effectively in inhibiting regulatory mutations or RT mutations did not significantly inhibit enzymatic site or EST mutations associated with SAHM (see abstract, pg. 1741). Importantly, Ma et al. demonstrated that mast cell lines with EST mutations was not inhibited by STI571 suggesting that the kit inhibitor STI571 is effective against certain mastocytosis and not SAHM (see abstract pg. 1741). This suggests that certain mastocytosis is resistant to imatinib.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to try the midostaurin of Longley in sporadic adult-type mastocytosis since Goekjian teaches that midostaurin is a potent inhibitor of c-kit with low toxicity properties. Given the teachings of Longley, Goekjian, and Ma, one of ordinary skill

would have been motivated to try midostaurin in light of the disclosures of Goekjian, Longley, and Ma with the reasonable expectation of providing a method effective in treating sporadic adult type mastocytosis and imatinib-resistant mastocytosis with a potent and low toxicity staurosporine derivative.

Claims 21-28, 31-33, and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Longley et al. (Hematology/Oncology Clinics of North America,, Vol. 14, No. 3, pgs. 689-695, previously cited) in view of Goekjian et al. (Experts Opinions on Investigational Drugs, December 2001, Vol. 10, No. 12, pgs. 2117-2140, previously submitted) as applied to claim 20 above and in further view of Ma et al. (Blood, 2002, Vol. 99, No. 5, pgs. 1741-1744, previously cited) as applied to claims 30 and 34 and in further view of Caravatti et al. (U.S. 5,093,330, previously cited).

The Goekjian and Longley references are as discussed above and incorporated by reference herein. However, Goekjian and Longley do not teach the forms of the composition, the exact dosage of midostaurin to be used in the treatment of mastocytosis or the mode of administration.

Caravatti et al. teach N-substituted derivatives of staurosporine including N-benzoyl-staurosporine (see abstract and col. 28, lines 45-57). Specifically, Caravatti teaches that the pharmaceutical compositions containing the aforementioned active

ingredients can be administered enterally, perorally (i.e. orally), or rectally wherein the peroral administration is in an amount of 5-500 mg (see col. 23, lines 21-29). Caravatti et al. further teach that the aforementioned active ingredients can be administered in an effective amount in a daily dosage from 1 to 1000 mg depending on the species, body weight, age, individual conditions, desired method of administration and the type of disease (see col. 23, lines 3-29). Additionally, Caravatti et al. teach that the composition can be formulated as soft sealed capsules containing gelatin and plasticizers (i.e. soft gel; instant claims; see col. 23, lines 57-68 and col. 24, lines 1-11). Caravatti et al. further teach that the aforementioned pharmaceutical preparations can be formulated in a manner known per se (col. 24, lines 22-25). As for the mode of administration, the Examiner contends that it would be well within the purview of the skilled artisan to administer midostaurin at least daily for at least one week, discontinue the treatment if patient improves, and subsequently restarting treatment as desired during the course of experimentation depending on the desired treatment as taught by Caravatti et al.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to vary the mode of administration and treat mastocytosis in the range of 1 to 1000 mg or 5-500 mg for peroral administration since Caravatti et al. teach that one of ordinary skill in the art can vary the concentration depending on the desired mode of administration, disease, and the patient to be treated. Thus, given the teachings of Goekjian, Longley, Ma and Caravatti et al., one of ordinary skill would have

been motivated to utilize midostaurin and vary the dosages and mode of administration in light of the disclosures of Goekjian, Longley, Ma and Caravatti with the reasonable expectation of providing a method effective in treating mastocytosis with a potent and low toxicity staurosporine derivative.

Claims 29 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Longley et al. (Hematology/Oncology Clinics of North America,, Vol. 14, No. 3, pgs. 689-695, previously cited) in view of Goekjian et al. (Experts Opinions on Investigational Drugs, December 2001, Vol. 10, No. 12, pgs. 2117-2140, previously submitted) as applied to claim 20 above and in further view of Ma et al. (Blood, 2002, Vol. 99, No. 5, pgs. 1741-1744, previously cited) as applied to claims 30 and 34 and in further view of Caravatti et al. (U.S. 5,093,330, previously cited) as applied to claims 21-28, 31-33, and 35-38 in further view of Matthews et al. (U.S. 2002/0061873).

The Longley, Goekjian, Ma, and Caravatti references are as discussed above and incorporated by reference herein. However, Longley, Goekjian, Ma, and Caravatti do not teach the composition as a microemulsion.

Matthews et al. teach N-benzoyl staurosporine (i.e. midostaurin or PKC 412) compositions with high bioavailability (see abstract). Matthews et al. further teach that

the pharmaceutical formulations produce aqueous microemulsions which are stable for up to one day or longer (see pg. 5, paragraph 0067).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to formulate the composition as a microemulsion since Matthews et al. teach that midostaurin can be made as aqueous microemulsions that are stable for up to one day or longer. Thus, given the teachings of The Longley, Goekjian, Ma, and Caravatti et al., one of ordinary skill would have been motivated to formulate midostaurin as a microemulsion with the reasonable expectation of providing a method effective in treating mastocytosis with a potent, stable and low toxicity staurosporine derivative.

(10) Response to Argument

(1) Appellant asserts that the present invention is not prima facie obvious because the references do not provide a finite number of identified, predictable solutions to the problem solved and because the prior art would not lead the skilled artisan to have a reasonable expectation of success. Additionally, Appellant asserts that the record does not provide any basis to expect that a compound which inhibits wild type KIT (or kit) would inhibit D816V KIT.

The Examiner disagrees because Longley in view of Goekjian does indeed render prima facie obvious applicant's invention. Specifically, Longley teaches that studies have shown that mutations affecting the protein coding region of the c-kit proto-oncogene are known to cause some forms of mastocytosis. Additionally, Longley teaches that activating mutations have been found in neoplastic mast cells of patients

with mastocytosis thereby implicating c-kit in the causation of the disease. As a result, Longley proposes that inhibition of activating-kit with kit inhibitors should therapeutically be useful in the treatment of mastocytosis. In fact, Longley teaches that studies tested various c-kit (i.e. kit or KIT) inhibitors and found that the various inhibitors were variably effective in inhibiting both wild-type kit and kit with activating mutations (see pg. 691). While the kit-inhibitors were not all potent in their inhibition, all inhibitors exerted some effects on the kit-tyrosine kinase and caused a reduction in c-kit's phosphorylation. This suggests to one of ordinary skill in the art that kit-inhibitors should help in alleviating the activation of the c-kit receptor and one of ordinary skill in the art would have indeed expected some successful results since Longley demonstrated some level of inhibition of both wild type and mutated KIT among the various c-kit inhibitors tested.

Given that Longley did not teach the use of midostaurin or PKC412 as the kit-kinase inhibitor in the treatment of mastocytosis, Goekjian was provided to demonstrate why one of ordinary skill in the art would have found it obvious to try and obvious to utilize PKC-412 as the kit-inhibitor in the treatment of mastocytosis as taught by Longley. Goekjian teaches that midostaurin or PKC412 is a first generation staurosporine analog that has been found to inhibit c-kit. Particularly, PCK412 or midostaurin was found to achieve greater level of kinase selectivity (i.e. c-kit selectivity) and potential therapeutic index and tended to be non-toxic. Consequently, the Examiner contends that one of ordinary skill in the art would have found it obvious to try PKC412 as the c-kit inhibitor in the treatment of mastocytosis since Longley teaches that c-kit inhibitors can be effectively used to treat mastocytosis and is expected to work

to a certain degree and in view of Goekjian who teaches that PKC412 is a selective c-kit inhibitor known to be therapeutically effective and non-toxic. In light of such disclosures, the Examiner maintains that Longley in view of Goekjian does indeed render obvious applicant's invention.

As for Appellant's argument that the record does not provide any basis to expect that a compound which inhibits wild type KIT (or kit) would inhibit D816V KIT, the Examiner contends that because Longley demonstrated the use of various Kit inhibitors in reducing the activity of both wild type and mutated Kit one skilled in the art would have found it obvious to try the selective Kit inhibitor, midostaurin, to treat mastocytosis given that Longley teaches that mastocytosis is characterized by a D816V mutation and given that Longley demonstrated that various analogous Kit inhibitors were variably effective in inhibiting both wild type and mutated Kit. The Examiner again reiterates the fact that treatment does not signify 100% inhibition. Additionally, the Examiner reminds appellant that nowhere in the specification did applicant require that treatment be equated to 100% inhibition. Attention is also directed to figure 2B of Longley which clearly demonstrated as compared to untreated mutant cells, all kit inhibitors caused a decrease in cell proliferation and thus would alleviate mastocytosis. Thus, given that Longley demonstrated that the various Kit inhibitors were effective in reducing phosphorylation in figure 1 and given that increased phosphorylation is associated with increased activity and thus disease causation, one skilled in the art would have found it obvious to utilize the selective inhibitor midostaurin/PKC 412 and obvious to conclude that any amount of reduction in Kit's phosphorylation by such compound would be

useful in attenuating the effects of mastocytosis. As a result, the Examiner maintains that the data of Longley, contrary to appellant's arguments, suggest that various kit inhibitors exert various effects on kit kinase and that such inhibitors are effective against both wild type and mutated kit kinases.

> (2) Appellants submit that Longley would not lead a skilled artisan to generally expect that inhibitors of wild-type Kit would provide a therapeutic benefit in mastocytosis. Additionally, Appellants submit that inhibitors of wild type kit would not provide a therapeutic benefit in mastocytosis as taught by Ma and that Longley's teachings are merely a general suggestion for further research. Moreover, Appellant argues that the Examiner failed to provide a finite number of identified, predictable solution.

The Examiner again disagrees with appellant as the Examiner maintains that Longley provides the basis to one skilled in the art to use kit inhibitors in inhibiting both wild-type kit and mutant kit kinases. Again, the Examiner refers Appellant to figure 1 which clearly shows that inhibitors of kit that were effective in suppressing tyrosine phosphorylation in the wild-type cells (WT) were also effective in inhibiting tyrosine phosphorylation in the mutant cells (C2 and P-815) though less robust. Such results would therefore suggest to one skilled in the art to try other kit inhibitors including the selective inhibitor midostaurin to inhibit kit's activation and thus treat mastocytosis as taught by Longley and have a reasonable expectation of success since Longley demonstrated that kit inhibitors were effective in inhibiting both WT and mutant KIT and in view of Goekjian who teaches that the compound midostaurin possesses low toxicity and is highly selective against Kit kinase. As for appellant's argument that a finite number of solutions was not provided, the Examiner again disagrees as the Examiner

maintains that a finite number of solutions were indeed provided as Longley teaches the use of indolinone derivatives to inhibit phosphorylation of KIT and thus treat the disease. Goekjian, on the other hand, teaches the indolinone derivative midostaurin and that such compound is highly selective for the KIT kinase and has low toxicity. Consequently, one skilled in the art would have indeed found it obvious to try the indolinone derivative of Goekjian to treat mastocytosis since Longley demonstrated that indolinone derivatives were effective in inhibiting both wild type KIT and mutant ones as well. Finally, regarding treatment of imatinib resistant cells, the Examiner maintains that given that Ma teaches certain forms of mastocytosis are resistant to imatinib, and given that Goekjian teaches that the indolinone derivative PKC 412 or midostaurin is highly selective for KIT, one of ordinary skill in the art would have found it obvious to try the highly selective Kit inhibitor midostaurin and would have had a reasonable expectation of success since other indolinone derivatives were found to be effective in inhibiting KIT activity (as demonstrated by Longley) and thus effective in the treatment of mastocytosis.

(3) Appellants submit that the instant invention fulfills a long felt but unsolved need. Additionally, Appellants argues that the evidence of record demonstrates unexpected benefits.

The Examiner again disagrees as the Examiner maintains that the need referred to by appellant was already suggested in the prior art. The Examiner respectfully points out that long felt need must have been a persistent one that was recognized by those of ordinary skill in the art. *In re Gershon*, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA

1967). Additionally, such long-felt need must not have been satisfied by another before the invention by applicant. In this instance, however, the Examiner contends that while at one time there was a long felt need for effective treatment for mastocytosis, the prior art clearly suggested the use of indolinone derivatives to suppress the activity of KIT kinase that would thus lead to treating the aforementioned disease. Again, the Examiner reiterates the fact that treatment does not mean curing of the disease but rather encompass alleviation or attenuation of the disease. Consequently, given that the prior art suggested the same type compounds as the instant invention the Examiner maintains that one of ordinary skill in the art would have indeed followed the teachings of the prior art in order to treat mastocytosis. While appellant argues that Goetlieb, Growney, and Gleixner described the use of midostaurin for the treatment of mastocytosis, the Examiner respectfully points out that such arts were not available at the time of the invention. Goekjian (provided by the Examiner), however, was published before the instant invention and suggested that midostaurin is a selective potent inhibitor and inhibits c-kit (i.e. KIT) at approximately micromolar concentration (see Goekjian, pg. 2123, right col., last paragraph, pg. 2124 and table 1). As a result of such disclosure, the Examiner contends that one of ordinary skill in the art at the time of the invention would have found it obvious to try midostaurin for treating mastocytosis since Longley teaches that constitutively active c-kit (i.e. constant activation of the kinase KIT) causes mastocytosis due to mutation and given that Longley demonstrated that indolinone derivatives (i.e. such genus includes midostaurin) were effective in inhibiting the activity of c-kit and thus effective against mastocytosis, and given that Goekjian

teaches that midostaurin is effective against KIT or c-kit at micromolar concentration. Consequently, the Examiner maintains that the long felt need proffered by Appellant was not unmet but was rather addressed by the disclosures of Longley and Goekjian.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Conferees:

/Shenjiun/

/Samira Jean-Louis/

Examiner, Art Unit 1627

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